REMARKS

Claims 1-21 are rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over U.S. Patent 5,178,868 (Malmqvist-Granlund et al.). Claims 1-21 are also rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over U.S. Patent 4,713,248 (Kjorn es et al.). Applicants respectfully traverse these rejections.

The Office Action has failed to make a *prima facie* case for obviousness with respect to Malmqvist-Granlund et al. and Kjorn es et al.

The release of active ingredient in the presently claimed invention has been delayed by one or more features, e.g., by the compaction of the core, by the inclusion of a polymer in the core, said polymer in the core being insoluble gastric and intestinal juices, and by providing a coating comprising a polymer insoluble in gastric and intestinal juices. The cited references, either alone or in combination, fail to suggest to those of ordinary skill in the art the presently claimed invention.

Malmqvist-Granlund et al. disclose an oral pharmaceutical controlled release multiple units dosage form in which individual units (cores) containing an active substance are surrounded by a coating essentially consisting of (a) a polymer that is insoluble and non-swellable in and impermeable to water and gastrointestinal fluids, and (b) a water-soluble pore-creating substance (cf. col. 1, lines 6-10; col. 2, lines 11-20 and 41-48; col. 3, lines 31-39).

Malmqvist-Granlund et al. do not teach or suggest to use, in the core of the coated particles, a polymer that is insoluble in gastric and intestinal fluids, nor do they teach or suggest to incorporate the active substance into a matrix of such a polymer. The specific teaching in the Examples of Malmqvist-Granlund et al. relates to crystals or non-pareils (apparently consisting of saccharose) with active substance applied to their surfaces, namely theophylline on non-pareils (Example 1), choline theophyllinate on sugar crystals (Example 2) and diltiazem hydrochloride on non-pareils (Example 3). The general teaching of Malmqvist-Granlund et al. confirms that the preferred cores are sugar crystals or pellets with active substance applied to their surface (cf. col. 4, lines 50-62); it is evident to those skilled in the art that these embodiments exclude any retarding effect regarding release of active substance from the core. Homogeneous cores in which the

active substance and the excipient(s) form a homogeneous mixture are mentioned only in a vague general remark stating that another type of pellets consists of substantially homogeneous particles prepared by wet-granulation or extrusion (cf. col. 4, lines 63-65). However, the use of polymers that are insoluble in gastric and intestinal juices (fluids) to delay the release of the active substance from the core, is not disclosed or suggested. Hence, Malmqvist-Granlund et al. do not suggest any means for delaying release from the core, let alone the present incorporation of the active substance into a matrix of a polymer insoluble in gastric and intestinal juices. The presently used polymers are preferably swellable and/or erodable, whereas those applied by Malmqvist-Granlund et al. must be non-swellable, such as non-swelling cellulose derivatives, acrylic polymers and vinyl polymers (cf. col. 4, lines 11-19). Besides, the polymers preferred in Malmqvist-Granlund et al. and exclusively used in the Examples are vinyl polymers.

Moreover, Malmqvist-Granlund et al. do not teach or suggest the present compaction of the core material to decrease its porosity compared to the porosities usually obtained after conventional methods such as granulation or extrusion. The decreased porosity in accordance with the present invention further delays release of the active substance from the cores. Malmqvist-Granlund et al. do not suggest any release-retarding means in connection with the cores, let alone the present decrease of their porosity. On the contrary, Malmqvist-Granlund et al. rather teach the use of release enhancing means, e.g., a water-soluble pore-creating material in the coating.

Malmqvist-Granlund et al. do not render obvious the combination of at least three release-delaying measures in accordance with the present invention – namely retardation in a matrix insoluble in gastric and intestinal juices, further retardation through compaction of the core material, and release-delaying coating – since they do not suggest any release-delaying measures for the core material and since their use of a pore-creating substance teaches away from the present invention.

Moreover, the presently claimed invention has a number of advantages, for example, high loadings of active ingredients are possible.

In the Examples of Malmqvist-Granlund et al., the pore-creating substance, sucrose, is used in large excess, namely in amounts of about 65% by weight, compared to

a polymer amount of about 25% by weight of the coating materials, thus confirming the reference to a sponge-like appearance. Those pores however facilitate release of the active substance through diffusion whereby the release-retarding effect of the polymer is decreased. The concept of Malmqvist-Granlund et al. therefore has, inter alia, the disadvantage that rather high amounts of excipients are required to achieve a reasonable release-retarding effect, as illustrated by Examples 1-3 in which the content of active substance in the coated cores was around 20% by weight or less. In contrast thereto, active substance contents of around 90% by weight are achievable in accordance with the present invention, as is illustrated in present Examples 1 and 5 (in which the active substance content of the coated particles was 88-89% by weight and the active substance content of the tablets was still far above 60% by weight). This is an advantage or superior property of the presented claimed invention.

Kjorn es et al. disclose an oral pharmaceutical controlled release multiple-units formulation in which individual units containing an active substance are coated with a substantially water-insoluble, but water-diffusible controlled release coating which includes (1) an inner film layer comprising a homogeneous combination of a water dispersible film-forming agent and a polymeric substance which imparts compressibility to the coating, and (2) optionally an outer film layer comprising a film-forming agent which prevents adhesion between the units at elevated temperatures and imparts flowability to the units (cf. col. 2, lines 38-51).

Kjorn es et al. do not teach or suggest to use, in the core of the coated particles, a polymer that is insoluble in gastric and intestinal fluids, nor do they teach or suggest to incorporate the active substance into a matrix of such a polymer. The specific teaching in the Examples of Kjorn es et al. relate almost exclusively to film-coated potassium chloride crystals (Examples 1-5 and 8) and tablets prepared therefrom (Example 6). Only Example 7 relates to the coating and tabletting of cores containing active substance (propranolol hydrochloride) and excipients. However, none of the excipients utilized in those cores is a polymer insoluble in gastric and intestinal juices, as is required in accordance with the present invention. Eudragit E 30 D is a 30% aqueous dispersion of Eudragit E which is not a polymer insoluble in gastric and intestinal juices, as discussed

at page 16, lines 6-15 of the present specification. The general teaching of Kjorn es et al. does not suggest the use of a polymer that is insoluble in gastric and intestinal fluids in the core of the coated particles. The passages from col. 5, line 48 to col. 6, line 19, and in col. 7, lines 18-45, merely state that the suitable cores are either crystals or pellets constituted of active substance and excipients, and refer to known "non-pareil" cores and known substantially homogeneous cores. Release-delaying measures are not suggested in this respect. In particular, Kjorn es et al. do not suggest to use, as a core excipient, a polymer that is insoluble in gastric and intestinal fluids, let alone the incorporation of the active substance into a matrix of such a polymer.

Further, Kjorn es et al. do not teach or suggest the present compaction of the core material to decrease its porosity compared to the porosities usually obtained after conventional methods such as granulation or extrusion but the general teaching merely states that the cores are typically made by granulation or by treatment in a planet mixer with subsequent extrusion (cf. col. 5, line 48 to col. 6, line 19; col. 7, lines 18-45). In Example 7, the moist mixture was extruded and then formed into cores in a marumerizer. As discussed above, the decreased porosity in accordance with the present invention further delays the release of the active substance from the cores. Kjorn es et al. do not suggest any release-retarding means in connection with the cores, let alone the present decrease of their porosity. Microcrystalline cellulose in Example 7 of Kjorn es et al., is a disintegrating agent commonly used to increase the dissolution rate of the drug. To illustrate this fact, enclosed are two sections from Ullmann's Encyclopedia of Industrial Chemistry. The use of microcrystalline cellulose in the cores of the known formulation does not suggest the present matrix retardation of the core but the accelerated dissolution is rather teaching away therefrom. Besides, Eudragit E 30 D used as a coating material and present also in a small amount in the cores of the formulation of Example 7 of Kjorn es et al. is not a polymer that is insoluble in gastric and intestinal juices (as already mentioned) and sodium carboxymethylcellulose present in a small amount in the cores and hydroxypropylmethylcellulose (Methocel) present in a small amount in the coating are disclosed among the water-soluble polymeric substances (cf. col. 3, lines 52-59). Hence, Example 7 of Kjorn es et al. does not teach or suggest present core matrix nor the

present coating; furthermore, the example does not teach or suggest the present compaction of the core material but the use of a disintegrant in the core rather teaches away from any release-delaying measures.

Furthermore, as discussed above, the controlled release coating in Kjorn es et al. includes an inner film layer and optionally an outer film layer. The inner film layer comprises a homogeneous combination of a water dispersible film-forming agent and a polymeric substance which imparts compressibility to the coating. The purpose of the film-forming agent is to enable a water-based film coating for environmental and process-economic reasons (cf. col. 2, lines 25-28). In the Examples, the (inner) coating is in each case based on Eudragit E 30 D, i.e. a 30% aqueous dispersion of the acrylic polymer Eudragit E which is not a polymer that is insoluble in gastric and intestinal juices (cf. page 16, lines 6-15 of the present specification) as required in accordance with the present invention. Kjorn es et al. merely state that the water-dispersible film-forming agent of Kjorn es et al. must be substantially water-insoluble but permit water diffusion, and mention some general classes of polymers from which suitable polymers might be selected, but they do not require that the polymer must be insoluble in gastric and intestinal juices, nor disclose anything in respect of their solubility in gastric and intestinal juices (cf. col. 3, lines 20-35).

Moreover, the inner film layer of Kjorn es et al. however also comprises a polymeric substance which is preferably a water-soluble polymeric substance selected from polyvinylpyrrolidones, polyalkylene glycols, cellulose derivatives (e.g. hydroxypropylcellulose such as Methocel used in the Examples), etc. Addition of the polymeric substance is allegedly capable of forming a continuous phase to the water-dispersible film-forming agent but its presence may reduce or even destroy the sustained release effect, if its amount is too high (cf. col. 2, lines 52-60 and col. 3, lines 46-68). Hence, the teaching of the inner coating layer in Kjorn es et al. does not suggest the present coating comprising a polymer that is insoluble in gastric and intestinal juices but the inner coating layer of Kjorn es et al. rather resembles the coating of Malmqvist-Granlund et al. in that both references teach the use of combination of a water-insoluble component and a water-soluble substance for coating the cores.

The optional outer film layer comprising a film-forming agent, which prevents adhesion between the units at elevated temperatures and imparts flowability to the units, is a protective layer applied in view of the problem that the inner layer may become tacky on heating (cf. col. 4, lines 35-60). The film-forming agent of the outer layer may be a diffusion coating material or an enteric coating material; the preferred film-forming agent is hydroxypropymethylcellulose although it is water-soluble and does not contribute to delaying release (cf. col. 4, line 61 to col. 5, line 33). Hence, neither of the coating layers of Kjorn es et al. suggests the present coating comprising a polymer that is insoluble in gastric and intestinal juices.

Kjorn es et al. do not suggest to those of ordinary skill in the art, the present combination of at least three release-delaying measures – namely retardation in a matrix insoluble in gastric and intestinal juices, further retardation through compaction of the core material, and release-delaying coating – since they do not suggest any release-delaying measures for the core material nor disclose the coating with a polymer insoluble in gastric and intestinal juices. The mere mention of cellulose esters an acrylic polymers and copolymers referred to by the Office Action could not disclose the latter feature, since the mere mention of those esters and polymers does not imply insolublility in gastric and intestinal juices and since the specifically used materials (such as hydroxypropymethylcellulose and the acrylic polymer Eudragit E) do actually not have this property (they are soluble), as discussed above.

The teaching of Kjorn es et al. resembles that of Malmqvist-Granlund et al. in that both references contain a similar disclosure for the cores and in that both references teach the use of mixture of a water-insoluble component and a water-soluble substance for coating the cores. Neither of the references suggests the present retardation of the core by incorporation of the active substance into a homogeneous mixture with a polymer insoluble in gastric and intestinal juices, nor do they suggest the present reduction of the porosity by compaction of the core material, nor do they disclose the present coating comprising a polymer insoluble in gastric and intestinal juices. Moreover, the cited references do not contain anything that could motivate the skilled person to modify the known compositions in a manner according to the present invention. In view of the re-

semblance of teachings of both references, even the combination of the teachings do not add anything to either reference to motivate one of ordinary skill in the art to create a pharmaceutical composition in accordance with the presently claimed invention.

As to the Office Action's remarks regarding the internal pore diameter and the percent porosity and the shifting of burden to applicants, it is respectfully submitted that the remarks are not founded on solid legal basis. An assertion of inherency should be made only when two conditions are satisfied: (1) the missing information must necessarily be present in the cited reference, and (2) one of ordinary skill in the art must recognize that the missing information is present in the reference. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 20 USPQ 2d 1746 (Fed Cir. 1991). Neither of the cited references teaches or suggests such compaction and the further release delaying advantage. Inherency may not be established by probabilities or possibilities. *Id* at 1749. In view of the differences and distinctness between the presently claimed invention and Malmqvist-Granland et al., and Kjorn es et al., the recited pore diameters and porosity are not necessarily presented in the cited references, and those of skill in the art would not recognize that the recited porosity or pore diameter would be present in the cited references. Moreoever, since the Examples disclosed in the cited references concern compositions in which the cores are either crystals of active substance or non-pareils with active substance applied to the surface rather than the present homogeneous mixture of active substance and polymer insoluble in gastric and intestinal juices, experimental evidence would not be necessary in view of the significant differences between the known and the presently claimed compositions, as set forth above. Nevertheless, the Office Action's attention is drawn to the fact that the cited references merely suggest granulation or extrusion in the case of pellets, and that this was not sufficient to achieve the desired low porosity but that additional compaction of the granulate at rather high pressure was necessary to obtain the advantages of the present invention. Typically about 5-30 kN/cm compaction forces are applied (see page 20-21 and examples). As disclosed on pages 8-9 of the present specification, the average internal pore diameter of conventional matrix granules is significantly above 35 μm and typically up to about 100

μm. Moreover, compaction usually increases the solid density of the core material by at least about 10% (Claim 2).

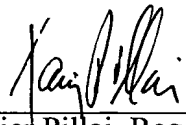
The presently claimed invention has one or more advantageous or superior properties. The present invention teaches a combination of at least three release delaying measures, namely by mixing the active ingredient with a polymer insoluble in gastric and intestinal juices (i.e. through formation of a particle matrix), through the small pore size due to compaction of the core material, and by coating the cores with a polymer insoluble in gastric and intestinal juices. The combination of those features enables one or more of a number of significant advantages not suggested by the cited art such as a release delaying that is substantially independent of the shape and size of the particles, a very efficient release delaying already with very low amounts of excipients, very high mechanical stability, an essentially unchanged release delaying when compressed into tablets, the release of active substance in a substantially pH-independent manner, the avoidance of large variations in the residence time in the stomach and the transit time through the intestinal tract, a decreased effect by aging and temperature variations, comparatively low production costs, and high reproducibility.

In view of all of the foregoing, the obviousness rejections of claims 1-21 should be withdrawn.

Conclusion

The application is considered in good and proper form for allowance.. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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